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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,816	03/27/2002	Michael Valentine Agrez	ADAM-046XX	9944

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,816	AGREZ ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *217-219,221,225,238,277,283 and 285-287* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *217-219, 221, 225, 238, 277, 283 and 285-287* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 284 has been canceled. Claims 217, 218, 238, 277, 283 and 285 have been amended. Claims 286 and 287 have been added. Claims 217-219, 221, 225, 238, 277, 283 and 285-287 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 217, 219, 225, 238, 285 and 286 encompass the treatment of cancer comprising the administration of SEQ ID NO:2, 3, 22 or 23 wherein the amino acids sequences of SEQ ID NO:2, 3, 22 or 23, or deletion mutant of SEQ ID NO:2, 22 or 23 are administered without a carrier peptide or auxiliary sequence to stabilize said peptide and facilitate cellular entry. The originally filed disclosure does not support the direct administration of SEQ ID NO:2, 3, 22 or 23 out of the context of a fusion protein (pages 54-55, bridging paragraph and final paragraph on page 55). One of skill in the art would reasonable conclude that applicant was not in possession of the claimed method at the time of filing.

Applicant has not addressed this rejection from the previous Office action (bottom of page 3).

Claims 217-219, 221, 225, 238, 277, 283 and 285-287 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the growth of a cancer cell comprising providing a binding domain comprising SEQ ID NO:2-5, 22 or 23, and a facilitator moiety in the context of a linear peptide, that facilitates the passage of the linear peptide across the cell membrane of the cancer cell, does not reasonably provide enablement for a method for inhibiting the growth of a cancer cell comprising providing a binding domain comprising SEQ ID NO:2-5, 22 or 23 without the facilitator domain, a method of treating cancer comprising administering a polypeptide comprising portions of SEQ ID NO:2-5, 22 or 23 with or without a linker sequence or with or without a facilitator domain or a method of inhibiting the growth of a cancer cell comprising the admisnintration of a binding domain

comprising SEQ ID NO:2-5, 22 or 23, a portion of a binding domain of SEQ ID NO:2-5, 22 or 23, wherein said binding domain or portion thereof is part of a cyclic peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

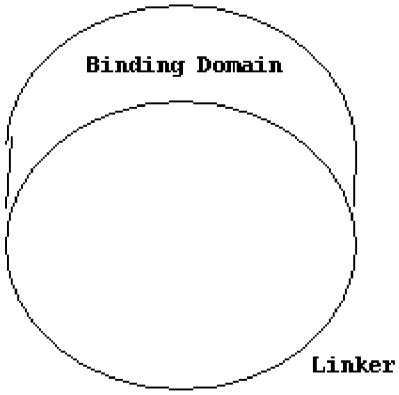
The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) Claims 217, 218, 221, 225, 238 are drawn to a method reliant on a genus of polypeptides that encompass amino acid sequences of the binding domains of SEQ ID NO:2, 22 and 23, essential for binding to a map kinase having a linker sequence which is non-essential fro binding of the MAP kinase which links opposite end regions of the binding domain together, and claims 277, 283, 286 and 287 are drawn to a method reliant on a genus of polypeptides that encompass deletion of amino acid sequences non-essential for binding to the MAP kinase from the binding domain of SEQ ID NO:2, 22 or 23.

The instant specification teaches that SEQ ID NO:2, 22 and 23 bind to the MAP kinase of Erk2. The specification teaches that the polypeptide will comprise the binding domain of the integrin, or sufficient core amino acid sequence of the binding domain to enable binding of the polypeptide with the MAP kinase (page 13, lines 1-3). The instant specification teaches RSKAKWQTGTNPLYR (SEQ ID NO:2) as a preferred embodiment, along with RSKAKNPLYR (SEQ ID NO:3) or one or both of RSKAK (SEQ ID NO:4) and NPLYR (SEQ ID NO:5). It appears that SEQ ID NO:3 represents SEQ ID NO:2 with a deletion of the amino acids WQTGT, and that SEQ ID NO:4 and 5 are the amino terminal and carboxyl terminal sequences of SEQ ID NO:2. Given that SEQ ID NO:2 is only 15 amino acids in length and the 5 amino terminal amino acids and 5 carboxyl terminal amino acids can bind to MAP kinase without the WQTGT sequence, one of skill in the art would be forced into undue experimentation without reasonable expectation of success to find further core fragments of SEQ ID NO:2 that can specifically bind to Erk2 because SEQ ID NO:4 and 5 are already down to 5

amino acids. The specification fails to teach other smaller fragments of a integrin binding domain that can function independent of the binding domain to specifically bind Erk2. The specification states that binding of Erk2 to the beta-5 and beta-3 peptides was also found (page 92, lines 10-11) but fails to state if the corresponding amino terminal or carboxyl terminal regions in the beta-5 and beta-3 peptides would function out of context of the binding domain to bind to Erk2. The specification teaches that the results of binding indicate a hierarchy of binding of Erk2 to integrin subunits (page 92, lines 12-14) but fails to state what the order is within the hierarchy. Further, Figure 34 is stated to represent the binding of erk2 to the instant SEQ ID NO:2 (beta-6), and corresponding regions of the cytoplasmic domains of beta-3 and beta-5, which do not bind to Erk2 to the same extent as RSKAKWQTGTNPLYR (binding region of beta-6). Thus, there is doubt that sub-regions of the binding domains from beta-3 and Beta-5 would necessarily retain specific binding to Erk2 because the entirety of the binding region does not bind as strongly to Erk2 as RSKAKWQTGTNPLYR (binding region of beta-6). Therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention with fragments of beta-6 that were not SEQ ID NO:4 and 5, fusion protein of SEQ ID NO:3, or subunits of the bindings domain of beta-3 and beta-5, linked together or not, with amino acids non-essential for binding to ERK2.

(B) Claims 217-219, 221, 225, 238, 277, 283 and 285-287 recite the limitation "an amino acid linker sequence that links opposite end regions of the binding domain together and which is non-essential for the binding to the MAP kinase". When given the broadest reasonable interpretation, the language of the instant claims217 and 286 include cyclic peptides:



wherein the linker sequence links opposite end regions of the binding domain together, such as in the drawing above. The specification contemplates on page 47, line 16 to page 48, line 8 that

A polypeptide or other agent may also be cyclised to provide enhanced rigidity and thereby stability in vivo. Various methods for cyclising peptides, fusion proteins or the like are known (eg Schiller et al, 1995). For example, a synthetic peptide incorporating two cysteeine residues distanced from each other along the peptide may be cyclised by the oxidation of the thiol groups of the residues to form a disulfide bridge between them. Cyclisation may also be achieved by the formation of a petpide bond between the N-terminal and C-terminal amino acids of the synthetic peptide or for instance through the formation of a bond between the positively charged amino groups on the side chan of a lysine residue and the negatively charged carboxyl group on the side chain of a glutamine acid residue. As will be understood, the position of the various amino acid residues between which such bonds are formed will determine the size of the cycle. Variation of cycle size for optimisation of binding affinity may be achieved by synthesising peptides in which the position of amino acids for achieving cyclisation has been altered. The formation of direct chemical bonds between amino acids or the use of any suitable linker to achieve cyclisation is also well within the scope of the skilled addressee.

The specification provides no examples of a cyclic peptide comprising an integrin ERK2 binding domain or a cyclic peptide comprising a portion of a ERK2 binding domain that retains

binding affinity to ERK2. As stated above, the size of the cyclic peptide can alter binding affinity, and as such there is no assurance that the brodaly contemplated binding domains, binding domains comprising deletions and binding domains comprising "non-essentail" linker sequences wwould function to bind to ERK2 and block the interaction between integrin beta-6 and ERK2 when present in the context of a cyclic peptide.

(C) Claims 217, 219, 225, 238, 285 and 286 encompass the treatment of cancer comprising the administration of SEQ ID NO:2, 3, 22 or 23 wherein the amino acids sequences of SEQ ID NO:2, 3, 22 or 23, or a substitution or deletion mutant of SEQ ID NO:2, 22 or 23 are administered without a carrier peptide or auxiliary sequence to stabilize said peptide and facilitate cellular entry. The art teaches that absent the targeting of a specific receptor which undergoes endocytosis, specialized peptide structures are required to traverse the cellular membrane, such as a signal sequence (Lin et al, Journal of Biological Chemistry, 1995, Vol. 270, pp. 14255-14258), a portion of a homeodomain peptide such as Antennapedia (Prochiantz et al, Proceeding of the NY Academy of Science, 1000, Vol. 886, pp. 172-179), or a pore-forming amphiphillic peptide, such as melittin (Yang et al, Biophysical Journal, 2001, Vol. 81, pp. 1475-1485). The prior art teaches that the conserved traits which allow for membrane penetration and transport into the cytosol were not understood at the time of filing (Prochiantz et a, ibid, page 177,under "Conclusion"). Further, the instant specification teaches on page 90, lines 6-8, that only the penetratin-peptide complex was effective in inhibiting cell proliferation in contrast to either peptide (the instant SEQ ID NO:2) or penetratin alone. Thus, the lack of knowledge of the membrane penetration characteristics of the instant claimed peptides, including SEQ ID NO:3-5, 22 and 23 and the deletion mutant peptides of claims 285 and 286 to traverse the membrane without assistance from a membrane-transport facilitating agent, such as the homeodomain peptide of Antennapedia would impart undue experimentation without reasonable expectation of success in order to carry out the claimed methods without aid of a facilitator moiety as required in dependent claims 218, 221, 277, 283 and 287.

All claims are rejected.

All other rejections and objections as set forth or maintained in the prior office action are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643